Direct Catalytic Asymmetric Synthesis of N-Heterocycles from Commodity Acid Chlorides by Employing α,β-Unsaturated Acylammonium Salts


Significance: An asymmetric enantioselective Michael addition–proton transfer–lactamation or lactonization organocascade reaction is reported. The cinchona alkaloid derived catalysts 1 can generate chiral α,β-unsaturated acylammonium salts with crotonyl chlorides 2, giving pyrrolidinones, piperid-2-ones, and dihydropyridinones in good yields and high enantioselectivities.

Comment: In the first step, the lithiated enolate is formed to participate in a conjugate addition to the acylammonium species, which derives from reaction of the chiral tertiary amine (R33N) with the acid chloride. After an intra- or intermolecular proton transfer, the acylammonium species undergoes intramolecular lactamation to regenerate the tertiary amine catalyst R33N. The products could be transformed into known precursors of various biologically active compounds.

Synthesis of Pyrrolidinones via α,β-Unsaturated Acylammonium Ions

Proposed catalytic cycle:

1a (20 mol%) LiHMDS (1.0 equiv) DBU (1.0 equiv) THF, 18 h, –30 °C

11 examples 40–88% yield en from 92.5:7.5 to 99.5:0.5

1b (20 mol%) LiHMDS (1.0 equiv) DBU (1.0 equiv) THF, 18 h, –30 °C

5 examples 48–84% yield en from 94.5:5.5 to 98.5:1.5